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Modeling study of mecamylamine block of muscle type acetylcholine receptors

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Abstract

The blocking action of mecamylamine on different types of nicotinic acetylcholine receptors (nAChRs) has been extensively studied and used as a tool to characterize the nAChRs from different synapses. However, mechanism of mecamylamine action was not fully explored for all types of nAChRs. In the present study, we provide brief description of the mecamylamine action on muscle nAChRs expressed at the frog neuromuscular junction. In this preparation mecamylamine block of nAChRs was accompanied by a use-dependent block relief induced by membrane depolarization combined with the activation of nAChRs by endogenous agonist acetylcholine (ACh). Further, three kinetic models of possible mecamylamine interaction with nAChRs were analyzed including simple open channel block, symmetrical trapping block and asymmetrical trapping block. This analysis suggested that mecamylamine action could be described on the basis of trapping mechanism, when the antagonist remained inside the channel even in the absence of bound agonist. Such receptors with trapped mecamylamine inside were predicted to have a closing rate constant about three times faster than resting one and a fast voltage-dependent unblocking rate constant. Specific experimental conditions and morphological organization of the neuromuscular synapses were considered to simulate time course of the mecamylamine block development. Thus, likewise for the neuronal nAChRs, the trapping mechanism determined the action of mecamylamine on synaptic neuromuscular currents evoked by the endogenous agonist acetylcholine (ACh), however specific morphological organization of the synaptic transmission delayed time development of the currents block.

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Keywords

Mathematical modeling, Mecamylamine, Muscular nicotinic acetylcholine receptors, Trapping block, Zonal organization of transmitter release